(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 2003/070909 A3

(51) International Patent Classification[7]: A61K 9/14, 9/16

(21) International Application Number:
PCT/US2003/005017

(22) International Filing Date: 20 February 2003 (20.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/358,315 20 February 2002 (20.02.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
31 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/070909 A3

(54) Title: MICROPARTICLES WITH ADSORBED POLYPEPTIDE-CONTAINING MOLECULES

(57) Abstract: Microparticles with adsorbed polypeptide-containing molecules formed without the use of surfactant, methods of making such microparticle compositions, and uses thereof, are disclosed. The microparticles comprise a polymer, such as a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and the like. Preferred polymers are poly(D,L-lactide-co-glycolides), more preferably those having a lactide/glycolide molar ratio ranging from 40:60 to 60:40 and having a molecular weight ranging from 20,000 Daltons to 70,000 Daltons. Preferred polypeptide containing molecules are bacterial and viral antigens (including HIV antigens, meningitis B antigens, streptococcus B antigens, and Influenza A hemagglutinin antigens).

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/05017

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC(7) : A61K 9/14, 9/16
US CL : 424/489, 490, 491
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/184.1, 204.1, 208.1, 489, 490, 491; 264/4.1; 514/772,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, MEDLINE, CAPLUS, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | JEONG et al., "Preparation of poly(DL-lactide-co-glycolide) nanoparticles without surfactant," Journal of Applied Polymer Science, 2001, Vol. 80, pages 2228-2236. | 1-9, 20, 22-29 |
| Y | JEON et al., "Effect of solvent on the preparation of surfactant-free poly(DL-lactide-co-glycolide) nanoparticles and norfloxacin release characteristics," International Journal of Pharmaceutics, 2000, Vol. 207, pages 99-108. | 1-9, 20, 22-29 |
| Y | SORIANO et al, "Use of surfactants in polylactic acid protein microspheres," Drug Developement and Industrial Pharmacy, 1995, Vol. 21 No. 15, pages 549-58, whole document. | 1-9, 20, 22-29 |
| Y | YANG et al., "Encapsulating aspirin into a surfactant-free ethyl cellulose microsphere using non-toxic solvents by emulsion solvent-evaporation technique," Journal of Microencapsulation, 2001, Vol. 18 No 2, pages 223-36, esp. pages 223-25. | 1-9, 20, 22-29 |
| Y | WO 98/33487 A1 (CHIRON CORPORATION) 06 August 1998 (06.08.1998), document, esp. pages 6-8, and 12-20. | 1-9, 20, and 22-29 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 04 November 2004 (04.11.2004) | 15 FEB 2005 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Zachariah Lucas<br>Telephone No. 571-272-1600 |

Form PCT/ISA/210 (second sheet) (July 1998)

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## INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | KAZZAZ et al., "Novel anionic microparticles are a potent adjuvant for the induction of cytotoxic T lymphocytes against recombinant p55 gag from HIV-1," Journal of Controlled Release, 2000, Vol. 67, pages 347-56. | 7-9, 20 |
| Y,P | US 6,383,470 B1 (FRITZSCH et al.) 07 May 2002 (07.05.2002), whole document, esp. columns 2-4. | 1-9, 20, 22-29 |
| A | US 5,858,410 A (MULLER et al.) 12 January 1999 (12.01.1999), whole document. | 1-9, 20, 22-29 |
| A | KAWASHIMA et al., "Properties of a peptide containing DL-lactide/glycolide copolymer nanospheres prepared by novel emulsion solvent diffusion methods," European Journal of Pharmaceutics and Biopharmaceutics, 1998, Vol. 45, pages 41-48. | 1-9, 20, 22-29 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/05017

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 10-19, 21, 30-35
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Please See Continuation Sheet

**Remark on Protest**
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/05017

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9, 20, and 22-29 (in part), drawn to microparticles comprising a poly (α-hydroxy acid), and with an HIV antigen adsorbed thereto, and a first method of making the particle.

Group II, claim(s) 1-9, 20, and 22-29 (in part), drawn to microparticles comprising a poly (α-hydroxy acid), and with a non-HIV antigen adsorbed thereto, and a first method of making the particle.

Group III, claim(s) 1, 7-9, 20, and 22-25 (in part), drawn to microparticles comprising a polyhydroxy butyric acid, and with an antigen adsorbed thereto; and to a first method of making the particles.

Group IV, claim(s) 1, 7-9, 20, and 22-25 (in part), drawn to microparticles comprising a polycaprolactone, and with an antigen adsorbed thereto; and to a first method of making the particles.

Group V, claim(s) 1, 7-9, 20, and 22-25 (in part), drawn to microparticles comprising a polyorthoester, and with an antigen adsorbed thereto; and to a first method of making the particles.

Group VI, claim(s) 1, 7-9, 20, and 22-25 (in part), drawn to microparticles comprising a polyanhydride, and with an antigen adsorbed thereto; and to a first method of making the particles.

Group VII, claim(s) 1, 7-9, 20, and 22-25 (in part), drawn to microparticles comprising a polycyanoacrylate, and with an antigen adsorbed thereto; and to a first method of making the particles.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

If the Applicant pays for an additional invention from Group II to be examined, the Applicant must also elect one of the inventions of (B)-(I) below.
If the Applicant pays for an additional invention from any of Groups III-VII to be examined, the Applicant must also elect one of the inventions of (A)-(I) below.

Species (A)-(F) relate to the claimed microparticles, wherein the polypeptide adsorbed to the surface is:

(A) an HIV antigen,
(B) a meningitis antigen,
(C) a streptococcus antigen,
(D) a hepatitis B antigen,
(E) a hepatitis C antigen,
(F) an Haemophilus influenza type B antigen,
(G) a pertussis, diptheria, or tetanus antigen,
(H) a Helicobacter pylori antigen, or
(I) an Influenza A hemagglutinin antigen.

The claims are deemed to correspond to the species listed above in the following manner:

Each of the species is independently claimed in claim 8.

The following claim(s) are generic: 1, and 22.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the common technical feature among the inventions is the making and use of a microparticle comprising no surfactants. Such microparticles are taught by the art. See e.g., Soriano et al. Drug Development and Industrial Pharmacy, 21(5): 549-58 (1995), and Yang et al., J Microencapsulation, 18(2): 223-36 (2001). Each of these references teaches the making of microparticles for drug delivery without using surfactant. The additional teachings of O'Hagan et al. (WO 98/33487) provide teachings that would render obvious the adsorption of proteins onto, rather than encapsulating them in, the particles. Because the art teaches the making and use of the microparticles without surfactants, the different Groups share no common special technical feature. Unity is therefore lacking.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the species lack unity for the same reasons as indicated above with respect to Groups I-VII. Each of the species relates to microparticles comprising an antigen directed against a different pathogen. Thus, the antigens in the species provide no common special technical feature.

**Continuation of Box II Item 4:**
1-9, 21, and 22-29 to the extent that the claims read on embodiments wherein the antigen is an HIV antigen.